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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
MARIE-CLAUDE GINGRAS and JUDITH F. MARGOLIN

Appeal 2007-3749[1]
Application 10/021,509
Technology Center 1600

Decided: March 31, 2008

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 3, 5, 11, 15, 16, and 40-42, all the claims remaining in the application. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard March 6, 2008.

BACKGROUND

"Inflammation is a cellular and vascular response to injury, which includes release of inflammatory mediators, vasodilation, exudation of plasma and migration of inflammatory cells to the injury site" (Spec. ¶ 4). "Important cellular components of the inflammatory response include polymorphonuclear leukocytes, mast cells, monocytes/macrophages and platelets" (Spec. ¶ 5).

"Although inflammation can contribute to healing by facilitating removal of necrotic tissue and by initiating repair, it is not always beneficial . . . Thus, there is a general appreciation in the medical community that down regulation of the inflammatory response is needed in multiple medical situations in which the immune response causes tissue damage or provokes an unwanted reaction" (Spec. ¶ 7).

"Monocytes/macrophages are a direct source of vasoactive mediators, such as prostaglandins, leukotrienes and platelet activating factor. Also, monocytes release cytokines, such as, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), to stimulate vascular invasion of the injured tissue and migration and proliferation of the mesenchymal cells that start the repair process" (Spec. ¶ 5). "Activation of these immune cells is receptor-specific" (Spec. ¶ 6).

Triggering Receptor Expressed on Myeloid cells (TREM-1) is a monocytic receptor of the Ig superfamily, expressed on blood neutrophils and monocytes, and upregulated by LPS (Spec. ¶ 6). "Triggering of TREM-1 induces neutrophil secretion of the inflammatory cytokine IL-8 and release

of . . . myeloperoxidase . . . In monocytes, the triggering of TREM-1 induces secretion of IL-8 and TNF-α cytokines" (Spec. ¶ 6).

The present Specification describes a soluble form of the TREM-1 receptor. According to the Specification, "[t]his soluble TREM-1 receptor could act as a down regulator by competing with the cell-surface TREM-1 receptor [for ligand,] allowing the cell to limit the amount of activating signal it is receiving from the extracellular environment, thus modulating the inflammatory response" (Spec. ¶ 7).

STATEMENT OF THE CASE

Claims

Claims 1, 3, 5, 11, 15, 16, and 40-42 are on appeal. As the claims have not been argued separately, and therefore stand or fall together, we select claim 1 as representative for the purpose of deciding all issues raised by this appeal. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 1 reads as follows:

> 1. A method of modulating an immune response comprising administering to an animal, in need thereof, a composition of soluble polypeptides with at least a portion of amino acids 1 to 136 of SEQ ID NO:2 or a polypeptide mimetic thereof, in an amount effective to modulate the levels of TREM-1 and/or TREM-1SV ligand binding activity whereby the immune response is modulated in the animal.

The claims stand rejected as follows

I. Claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as drawn to new matter.

II. Claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

III. Claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Wang.[2]

IV. Claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Ruben.[3]

FINDINGS OF FACT[4]

1. Membrane-bound TREM-1 is an activating receptor "expressed on blood neutrophils and monocytes and is up-regulated by LPS . . . [T]riggering of TREM-1 induces secretion of IL-8 and TNF-α cytokines" (Spec. ¶ 6). In order for membrane-bound TREM-1 receptor to mediate activating signals, the extracellular portion of the receptor must associate with its ligand, and with a separate signal transduction subunit, i.e., the cytoplasmic adaptor molecule DAP12 (Spec. ¶¶ 6, 100, 101; Figure 1).

2. Figure 4 of the Specification represents the nucleotide and predicted amino acid sequences of the TREM-1 receptor and the TREM-1 splice variant of the receptor, including the transmembrane domain (Spec. ¶ 27; Fig. 4).

3. "Three potential N-linked glycosylation sites and the transmembrane region [of TREM-1] are missing" in the soluble receptor (Spec. ¶ 70). "[W]ithout the transmembrane region, the cell-surface receptor is a soluble receptor" (Spec. ¶ 70).

4. SEQ ID NO:2 represents the 150 amino acid sequence of the soluble TREM-1 receptor splice variant of TREM-1 (Spec. ¶¶ 69, 70). "The first 136 amino acids of these 150 amino acids are identical to the TREM-1 first

[2] U.S. Patent 6,504,010 B1 to Wang et al., issued January 7, 2003.
[3] U.S. Patent 6,420,526 B1 to Ruben et al., issued July 16, 2002.
[4] Abbreviated "FF".

136 amino acids, but the last 14 amino acids are totally different" (Spec. ¶ 70).

5. "[T]wo cysteines potentially generating an intrachain disulfide bridge characteristic of an Ig-superfamily V type fold, are conserved" in the soluble receptor (Spec. ¶ 70). "[T]he consensus sequences potentially involved in generating a disulfide bridge" are shown in the small boxes in Figure 4, one starting immediately after amino acid 36, and the other ending immediately before amino acid 114 (Spec. ¶ 27; Fig. 4). Thus, according to the Specification, "TREM-1 contains one extracellular immunoglobulin-like domain" (Spec. ¶ 24), purportedly containing the site of ligand binding.

6. "It is known in the art that soluble forms of cell-surface receptors can down regulate or dampen the ligand mediated activation of cells by binding the ligand, thus making the ligand unavailable to the cell-surface receptor" (Spec. ¶ 102).

7. According to the Specification, "a receptor lacking the transmembrane domain is not able to transmit a signal to DAP12 and acts as a down regulator. It is envisioned that [soluble TREM-1] . . . down regulates the immune response by competing with full length TREM-1 receptor for the ligand that binds to TREM-1. . . . [and] limit[s] the amount of activating signal available to the fully functional receptor complex" (Spec. ¶ 101).

8. According to the Specification, "[i]t is envisioned that myeloid cell activation can be decreased by decreasing the activity of DAP12/TREM-1 complex by providing a compound that is a competitive inhibitor of the ligand to TREM-1" (Spec. ¶ 98).

9. Specifically, according to the Specification, "[i]t is envisioned that TREM-1 splice variant or a variant [i.e., a competitive inhibitor of the ligand to TREM-1] is a potential therapy for septic shock" (Spec. ¶ 175), and an experiment is proposed in which "[m]ice are injected intraperitoneally with different concentrations of LPS. TREM-1 splice variant polypeptide or other competitive inhibitor of the ligand for TREM-1 is administered to the animal at 1, 2, 4 and 6 hours after LPS administration" (Spec. ¶ 176), or "1 hr prior to LPS administration" (Spec. ¶ 177). "In both examples it is envisioned that the administration of the TREM-1 splice variant results in a down regulation of the inflammatory response preventing shock and death. Thus, administration of a soluble TREM-1 is [envisioned to be] a suitable therapy for the treatment of septic shock as well as other inflammatory diseases" (Spec. ¶ 178).

10. Axel Bouchon et al., *TREM-1 Amplifies Inflammation and Is a Crucial Mediator of Septic Shock*, 410 Nature 1103-1107 (April 26, 2001), is a reference discussed in the declaration of inventor Dr. Marie-Claude Gingras (submitted under the provisions of 37 C.F.R. § 1.132 and made of record May 27, 2004, hereinafter "Gingras Decl."). Briefly, Bouchon describes an experiment designed to test "whether a TREM-1 receptor decoy reduces inflammation and lethal shock in murine models of sepsis" (Bouchon 1104, col. 2). A fusion protein containing the extracellular domain of murine TREM-1 and the Fc portion of human IgG1 (mTREM-1/IgG1) was injected into the peritoneal cavity of mice one hour before the induction of endotoxaemia (*id.*). "76% of the mice treated with mTREM-1/IgG1 survived endotoxaemia as compared with 6% of control mice" (*id.*).

Furthermore, "mTREM-1/IgG1 was still protective when administered 1, 2, 4 and 6 h after LPS injection . . . Thus, soluble TREM-1 is effective even when injected after the outbreak of endotoxaemia" (Bouchon 1104, col. 2 to 1105, col. 1). "mTREM-1/IgG1 was effective against endotoxaemia even when the IgG1-Fc portion of the fusion protein was mutated to inhibit Fc receptor binding and complement fixation" (Bouchon 1105, col. 1).

11. Sebastian Gibot et al., *A Soluble Form of the Triggering Receptor Expressed on Myeloid Cells-1 Modulates the Inflammatory Response in Murine Sepsis*, 200 J. Exp. Med. 1419-1426 (December 6, 2004), was made of record September 12, 2005. Briefly, Gibot describes an experiment in which LP17, a 17 amino acid synthetic protein based on a highly conserved domain in the extracellular portions of murine and human TREM-1 (Gibot 1420, col. 1), "attenuate[d] cytokine production by human monocytes and protect[ed] septic animals from hyper-responsiveness and death" (Gibot Abstract).

12. According to Dr. Gingras, "the data presented by Bouchon et al. in Nature 410: 1103-1107, 2001 are representative data that would have resulted from our proposed experiments in the present application" (Gingras Decl. ¶ 5), in which "we proposed modulating inflammation in septic shock by administering a competitive inhibitor of the ligand for TREM-1" in ¶¶ 175-178 (Gingras Decl. ¶ 4).

13. The Specification teaches that the TREM-1 "'competitive inhibitor' includes variants of the TREM-1 receptor, for example, truncations, deletions, or substitutions which result in a soluble receptor" (Spec. ¶ 34).

14. Similarly, the Specification teaches that "the term functional equivalent includes truncations, deletions, insertions or substitutions of TREM-1 . . . which retain their function to antagonize the actions of the full-length, membrane bound TREM-1" (Spec. ¶ 35).

15. The Specification "contemplate[s] that structurally similar compounds may be formulated to mimic the key portions of [the] peptide or polypeptides of the present invention" and "[s]uch compounds, . . . termed peptidomimetics, may be used in the same manner as the peptides of the invention and, hence, also are functional equivalents" (Spec. ¶ 75).

16. The Specification teaches that "[d]eletion mutagenesis can be performed to confirm the specific region that is necessary to bind the ligand of TREM-1 and mediate the cellular response" (Spec. ¶ 105), but there is no evidence of record to indicate that the ligand for TREM-1, or its binding site within the immunoglobulin-like domain, was known at the time of the invention.

17. The Specification does not explicitly describe any competitive inhibitors that are "functional equivalents" or "peptidomimetics" of the soluble receptor.

Wang

18. Wang describes a polynucleotide, SEQ ID NO:1824, which encodes a polypeptide, SEQ ID NO:1825, identical to the present SEQ ID NO:2. According to Wang, SEQ ID NO:1825 is expressed in lung cancer cells, and is useful as a lung cancer marker, or as a therapeutic target (Wang, Abstract; col. 3, l. 2).

Ruben

19. Ruben describes Gene No: 159, which encodes a polypeptide, SEQ ID NO:478. SEQ ID NO:478 is identical to SEQ ID NO:2. Ruben also describes proteins comprising "at least 30 contiguous amino acid residues of amino acid residues 27 to 234 of SEQ ID NO:478" (Ruben, claim 25), and particularly mentions peptides spanning positions 24 to 35; 59 to 64; 71 to 78; 89 to 94; 141 to 151; 167 to 171; and 175 to 180 (Ruben, col. 140, ll. 7-11). According to Ruben, "the translation product of . . . [Gene No: 159] shares sequence homology with immunoglobulin heavy chain" (Ruben, col. 139, ll. 15-16), and this "homology to [the] immunoglobulin heavy chain variable region indicate[s] that . . . polypeptides corresponding to this gene are useful for making ligands to block specific antigens which cause certain disease[s]" (Ruben, col. 139, ll. 39-43). In particular, Ruben teaches that "the protein product of this clone would be useful for the diagnosis and treatment of a variety of immune system disorders" (Ruben, col. 139, ll. 44-46), "including arthritis, asthma, . . . sepsis, . . . host-versus-graft and graft-versus-host diseases" (Ruben, col. 139, ll. 56-63).

DISCUSSION

New Matter

The Examiner rejected claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as containing new matter.

According to the Examiner, the Specification and the claims "as originally [filed] only support a general recitation of polypeptide spliced variant[s] of TREM-1 of SEQ ID NO:2, in which several, 5 to 10, 1 to 5[,] 1 to 3, 2, 1 or no amino acid residues are substituted, deleted or added" (Ans.

16). The Examiner contends that the recitations "soluble polypeptides with at least a portion of amino acid 1 to 136 of SEQ ID NO:2 or any polypeptide mimetic thereof" and "amino acid 36 to 114 of SEQ ID NO:2" "represent a departure from the specification and the claims as originally filed" (Ans. 16).

To satisfy the written description requirement, the Specification need not contain the identical words used in the claims. *See Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). We find that the Specification, as originally filed, supports the disputed language.

The original claims were directed, at least in part, to modulating an immune response using competitive inhibitors of the ligand of TREM-1, wherein the "competitive inhibitor is a polypeptide comprising an amino acid sequence of SEQ ID NO:2" (original claim 8), or its "functional equivalent" (original claim 9). The Specification teaches that SEQ ID NO:2 represents the 150 amino acid sequence of "the soluble receptor splice variant" of TREM-1 (Spec. ¶ 69), and "[t]he first 136 amino acids . . . are identical to the TREM-1 first 136 amino acids" (Spec. ¶ 70) (FF 4). In addition, this region contains "the consensus sequences potentially involved in generating a disulfide bridge" (Spec. ¶ 27) "characteristic of an Ig-superfamily V type fold" (Spec. ¶ 70), purportedly the site of ligand binding (FF 5). These consensus sequences are enclosed in boxes in Figure 4 of the Specification, one beginning immediately after amino acid 36, and one ending immediately before amino acid 114 of SEQ ID NO:2 (FF 5). Thus we find that the disputed end-points of SEQ ID NO:2 are supported by the Specification as originally filed.

As to the "at least a portion of . . . SEQ ID NO:2" language, the Specification broadly teaches that "the 'competitive inhibitor' includes variants of the TREM-1 receptor, for example, truncations, deletions, or substitutions which result in a soluble receptor" (Spec. ¶ 34) (FF 13). Similarly, the Specification teaches that "the term functional equivalent includes truncations, deletions, insertions or substitutions of TREM-1 . . . which retain their function to antagonize the actions of the full-length, membrane bound TREM-1" (Spec. ¶ 35) (FF 14). We find that the language of the Specification adequately conveys the concept of a competitive inhibitor of TREM-1 comprising "at least a portion of . . . SEQ ID NO:2."

Finally, as to the "polypeptide mimetic" language, we note that the Specification "contemplate[s] that structurally similar compounds may be formulated to mimic the key portions of [the] peptide or polypeptides of the present invention" and "[s]uch compounds, . . . termed peptidomimetics, may be used in the same manner as the peptides of the invention and, hence, also are functional equivalents" (Spec. 75) (FF 15). Thus, we find that the language of the Specification adequately conveys that peptidomimetic competitive inhibitors were intended to be part of the invention.

The rejection of the claims under 35 U.S.C. § 112, first paragraph, as containing new matter, is reversed.

Enablement

The Examiner rejected claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

The Examiner contends that it would have required undue experimentation to modulate an immune response in vivo by administering a

composition comprising "*any* soluble peptide with at least a portion of amino acid[s] 1 to 136 of SEQ ID NO:2 or any polypeptide mimetic thereof" (Ans. 6).

Appellants contend that "[t]he mechanisms by which the polypeptide competes for the TREM-1 ligand is described throughout the specification" (App. Br. 10); "different TREM-1 molecules across species have been studied and . . . their ligand binding site is a common conservative region forming a loop binding domain created by a pair of disulfide bridges" (*id.*); "the claimed therapeutic action of the composition having this binding ligand activity is supported by the data" in Bouchon and Gibot (*id.*); thus, "[o]ne can practice the claimed invention because one can predict the therapeutic efficacy of the composition with TREM-1 ligand binding activity as long as it contains a portion of the TREM-1[splice variant] (see amino acids 1-136 of SEQ ID NO:2) that provides a therapeutic action" (*id.*).

We agree with Appellants with respect to polypeptides containing a portion of amino acids 1-136 of SEQ ID NO:2, but we agree with the Examiner's position with respect to peptide mimetics of SEQ ID NO:2.

The Specification teaches that cell surface TREM-1 receptor is up-regulated by LPS, and induces secretion of inflammatory cytokines upon ligand binding and association with DAP12 (FF 1); that amino acids 1 to 136 of SEQ ID NO:2 represent the extracellular, soluble TREM-1 receptor and this portion purportedly includes the ligand binding domain (FF 3, 4, 5); and that soluble TREM-1, like many other soluble receptors, would be expected to down-regulate the activity of the membrane-bound receptor (FF

6, 7), e.g., inflammation/septic shock (FF 9), by competing with membrane-bound TREM-1 for ligand binding (FF 7, 8). Moreover, the Specification describes experiments designed to confirm that the administration of soluble TREM-1 results in a down regulation of the inflammatory response in sepsis (FF 9). Finally, there is evidence of record that supports these expectations (FF 10, 11, 12).

Peptides containing "at least a portion of amino acids 1 to 136 of SEQ ID NO:2" necessarily comprise defined sequences identical to stretches of SEQ ID NO:2. We do not agree with the Examiner that it would have required undue experimentation for one of skill in the art to make and test a series of peptides duplicating portions of SEQ ID NO:2 for the ability to modulate an immune response, following the protocols set forth in the Specification. Thus, we agree with Appellants that the Specification is enabling for modulating an immune response in vivo by administering a composition comprising a a soluble peptide with at least a portion of amino acid[s] 1 to 136 of SEQ ID NO:2.

However, we agree with the Examiner that it would have required undue experimentation to make and use polypeptide mimetics of SEQ ID NO:2 in order to modulate an immune response in vivo.

The Specification indicates that the term "peptidomimetics" is extremely broad, and encompasses any "structurally similar compounds . . . formulated to mimic key portions" of SEQ ID NO:2 (Spec. ¶ 75; FF 12), but no such peptide mimetics are described (FF 17). Moreover, the only guidance in the Specification regarding the "key" portion of SEQ ID NO:2 is the identification of a purported V region spanning amino acids 36 to 114

(FF 5), and there is no evidence that the TREM-1 ligand, or the exact location of its binding site within the loop domain, was known at the time of filing (FF 16). Thus, we agree with the Examiner that the Specification provides insufficient guidance "as to which core structure of SEQ ID NO:2 is essential to modulate an immune response and which changes can be made in the structure of SEQ ID [NO:]2 and still maintain[ ] the same function" (Ans. 10), especially as that function involves ligand binding (FF 7), and there is no evidence of record that the TREM-1 ligand, or its exact binding site, was known at the time of the invention (FF 16).

We conclude that the Specification is not enabling for modulating an immune response in vivo using polypeptide mimetics of SEQ ID NO:2. Accordingly, the rejection of claim 1 as lacking enablement under the first paragraph of 35 U.S.C. § 112, is affirmed, and claims 3, 5, 11, 15, 16, and 40-42 fall accordingly.

Anticipation by Wang

Claims 1, 3, 5, 11, 15, 16, and 40-42 stand rejected under 35 U.S.C. § 102(e), as anticipated by Wang.

Wang describes SEQ ID NO:1825, which is identical to SEQ ID NO:2. According to Wang, the protein of SEQ ID NO:1825 is expressed in lung cancer cells, and is useful as a diagnostic marker for lung cancer or as a therapeutic target (Wang, Abstract; col. 3, l. 2; FF 18).

We agree with Appellants that Wang does not anticipate the claimed invention as the reference does not teach administering a polypeptide of SEQ ID NO:1825 to an animal.

The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Wang is reversed.

Anticipation by Ruben

Claims 1, 3, 5, 11, 15, 16, and 40-42 stand rejected under 35 U.S.C. § 102(e), as anticipated by Ruben.

Appellants argue that Ruben "is very vague" (App. Br. 12), and "lacks any real disclosure that would put into the public's possession the claimed methods" (App. Br. 13). According to Appellants, Ruben "merely describes an expressed sequence tag (EST) DNA sequence, among many others, including a matching sequence of TREM-1sv" (App. Br. 13), but "does not indicate which one or which combination of the sequence SEQ ID NO 478 being presented in seven different epitopes, must be used to produce a polypeptide usable as a protein therapeutic to modulate an immune response" (App. Br. 13).

This argument is not persuasive. Ruben describes SEQ ID NO:478, a protein identical to SEQ ID NO:2, as well as peptides comprising "at least 30 contiguous amino acid residues of amino acid residues 27 to 234 of SEQ ID NO:478." In addition, Ruben describes peptides spanning positions 24 to 35; 59 to 64; 71 to 78; 89 to 94; 141 to 151; 167 to 171; and 175 to 180. Ruben teaches that SEQ ID NO:478 shares sequence homology to the variable region of immunoglobulin heavy chain, and that the protein would be useful for the diagnosis and treatment of a variety of immune system disorders, including sepsis (FF 19). Thus, Ruben teaches administering polypeptides comprising portions of SEQ ID NO:478, and at least some of these would correspond to portions of the soluble TREM-1 receptor.

The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Ruben is affirmed.

SUMMARY

I. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as drawn to new matter, is reversed.

II. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 112, first paragraph, as lacking enablement, is affirmed.

III. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Wang is reversed.

IV. The rejection of claims 1, 3, 5, 11, 15, 16, and 40-42 under 35 U.S.C. § 102(e), as anticipated by Ruben is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

ssc:

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